Amendments to the Specification

Please amend paragraphs [0012] and [0013], on pages 4 to 5, as follows:

[0012] Several different nicotine haptens, carriers and methods of coupling have been described. Matsushita et al. (Biochem. Biophys. Res. Comm. (1974) 57, 1006-1010) and Castro et al. (Eur. J. Biochem. (1980) 104, 331-340) prepared nicotine haptens conjugated to bovine serum albumin (BSA) via a linker at the 6-position of the nicotine. Elsewhere, Castro *et al.* (Biochem. Biophys. Res. Commun. (1975) 67, 583-589) disclosed two nicotine albumin conjugates: N-succinyl-6-amino-(+/-)-nicotine-BSA and 6-(sigma-aminocapramido)-(+/-)-nicotine-BSA. Noguchi et al. (Biochem. Biophys. Res. Comm. ~~(1975)~~ (1978) 83, 83-86) prepared a nicotine-BSA conjugate with nicotine conjugated at the 1-position of the nicotine. Langone et al. (Biochemistry (1973) 12, 5025-5030 and Meth. Enzymol. (1982) 84, ~~628-635~~ 628-640) prepared the hapten derivative O-succinyl-3'-hydroxymethyl-nicotine and conjugated it to bovine serum albumin and keyhole limpet hemocyanin. According to the procedures of Langone et al.(supra), Abad et al. (Anal. Chem. (1993) 65, 3227-3231) synthesized the nicotine hapten 3'-(hydroxymethyl)-nicotine hemisuccinate and coupled it to bovine serum albumin for immunization of mice to produce monoclonal antibodies to nicotine. Isomura *et al.* (J. Org. Chem. (2001) 66, 4115-4121) provided methods to synthesize nicotine conjugates linked to the 1'-position of nicotine, which were coupled to keyhole limpet hemocyanin (KLH) and BSA. The conjugate to KLH was used to immunize mice and to produce monoclonal antibodies against nicotine.

Svensson *et al.* (WO 99/61054) disclosed nicotine-haptens conjugated via the pyridine ring and further disclosed a nicotine-hapten conjugated to KLH and the induction of nicotine-specific IgG antibodies using such conjugates. When administered in the presence of complete Freund's adjuvant, nicotine-specific ELISA titres of 1: 3000 to 1: 15500 were measured, while in the absence of Freund's adjuvant titres of 1:500 to 1:3000 were detected. Ennifar *et al.* (U.S. Patent No. 6,232,082) disclosed nicotine haptens coupled via the pyrrolidine ring and disclosed a nicotine-hapten conjugated to recombinant *Psuedomonas aeruginosa* exotoxin A (rEPA) and the induction of nicotine-specific IgG antibodies when the conjugates were administered in the presence of complete Freund's adjuvant. Swain et al. (U.S. Patent No. 5,876,727) disclosed the coupling of a nicotine hapten to BSA and the induction of nicotine-specific IgG antibodies in mice when the conjugates were given in a mixture with complete Freund's adjuvant.

[0013] The feasability of a vaccination against nicotine has been shown in principle (Hieda *et al., J. Pharm. Exp. Ther.* (1997) ~~288~~ 283, 1076-1081; Hieda *et al., Psychopharm.* (1999), 143, 150-157 ; Hieda *et al., Int. J. Immunopharm.* (2000) 22, 809-819; Pentel *et al., Pharm. Biochem. Behav.* (2000), 65, 191-198, Malin *et al, Pharm. Biochem. Behav.* (2001), 68, 87-92). Covalent conjugates of nicotine with KLH or rEPA were produced and injected into mice or rats in the presence of complete Freund's adjuvant, and induced nicotine-specific IgG antibodies. Vaccine efficacy was demonstrated by several different ways. After challenge with nicotine, more nicotine remained bound in serum and nicotine concentrations were lower in the brain in the nicotine-KLH or nicotine-rEPA immunized groups of rats compared to the control group immunized with carrier alone. Immunization also reduced the psychopharmacological activity associated with nicotine, as immunized animals were also

less susceptible to the effect of nicotine on locomoter activity, dopamine release (Svensson *et al.* WO 99/61054) and relief of nicotine withdrawal symptoms.

Please amend paragraph [0228], on page 66, as follows:

[0228] In a related embodiment, 3'-linkages to nicotine haptens are performed by first generating trans-3'-hydroxymethylnicotine which is reacted with succinic anhydride to yield the succinylated hydroxymethylnicotine (O-succinyl-3'-hydroxymethyl-nicotine). This product is then mixed with EDAC and the core particle for carbodiimide-activated coupling, as described by Langone and Van Vunakis (*Methods Enzymol.* 84:~~629-641~~ 628-640 (1982)) the reference to which is incorporated herein in its entirety. In another embodiment, trans-4'-carboxycotinine is similarly activated with EDAC for coupling to a protein carrier.